EXHIBIT D

VOLUME I – FULL TECHNICAL PROPOSAL

1. COVER PAGE

BAA Number: FY23C3DWP3

Title of Proposal: Health and Neurodevelopmental Outcomes in Infants at Risk for Neonatal Opioid Withdrawal Syndromes (NOWS): Effects of Timing and Duration of Prenatal Opioid Exposure (POE) & Postnatal Management with Eat-Sleep-Console (ESC)

Prime Offeror: Lena S. Sun, MD

Topical Area: # III.D. 1.2.d: Develop methods and carry out studies to better understand the trajectory of use of controlled substances and associated public health consequences

List of Subcontracts: (1) Kaiser Permanente Northern California
(2) University of California at Berkeley

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Duration of Effort: 48 months

2. OFFICIAL TRANSMITTAL LETTER

COLUMBIA UNIVERSITY MEDICAL CENTER

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May 22, 2023

Ms. Ingrid Walker
Contracts Specialist, Scientific Support Branch
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Re: Official Transmittal Letter

Dear Ms. Walker:

On behalf of The Trustees of Columbia University in the City of New York, please find enclosed the referenced contract bid in response to FDABAA-23-00123 from Dr. Lena Sun.

I confirm that I am an Authorized Organizational Representative of Columbia University and furthermore confirm that I have the authority to propose to Government solicitations and compete with industry, and their compliance with the associated sponsoring agreement and terms and conditions.

If you should need any additional information, please contact me at grants-office@columbia.edu or 212-305-4191.

Regards

Madhavi Nambiar

Madhavi Nambiar, PhD
Associate Director of Research Operations
Sponsored Projects Administration

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4. EXECUTIVE SUMMARY

In alignment with the objectives of FDA to apply regulatory science to ensure optimal drug safety in pediatric populations, the proposed project will address the critical public health consequences of prenatal opioid exposure during the ongoing opioid epidemic in the US. The proposal will specifically compare differences in outcomes (both in-hospital and neurodevelopmental outcomes) between opioid replacement pharmacotherapy and non-pharmacological management in infants with neonatal opioid withdrawal syndrome (NOWS).

- Hypothesis

We will test the hypothesis that non-pharmacological approach to manage NOWS infants, including the use of “Eat, Sleep, Console (ESC)”, improves their in-hospital and neurodevelopmental (ND) outcomes compared to opioid replacement treatment. We will further test the hypothesis that timing, duration and doses of prenatal opioid exposure are modifiers of the effects of non-pharmacological management on in-hospital and ND outcome in NOWS infants such that better outcomes are most evident in infant with sustained opioid exposures for eight or more weeks or in infants who had prenatal opioid exposure that included first or second trimester.

- Data Source

The proposed study will use the Kaiser Permanente Northern California (KPNC) research databases as the data source. The KPNC research databases (herein referred to as KPNC database) consist of multiple databases, and they are a repository for KPNC clinical and administrative databases from legacy and KP HealthConnect® (KPHC). For the proposed study, data will be captured using the following KPNC databases: Infant Cohort (IC), Virtual Data Warehouse (VDW), KPNC laboratory database (LURS), and Clarity. Only data sources derived from KP HealthConnect® (KPHC) will be used. KPHC is an integrated electronic health record (EHR) system designed by the Epic Systems Corporation (Verona, WI) with the following major Epic modules: (1) Ambulatory/Outpatient (2) KP HealthConnect Online and (3) Inpatient. The KPNC databases provide comprehensive and high quality administrative and clinical data on a large and diverse patient population. KPNC program participants come from a very diverse geographic, racial, ethnic, and socioeconomic background. Infants born within KPNC (birth cohorts) can be tracked longitudinally and are linked to the mothers, providing excellent assessment of maternal risk factors. The KPNC databases include detailed pharmacy records and clinical data from all inpatient and outpatient encounters in the EHR, so details of both exposures and outcomes in our proposed study can be further validated and verified. In addition, data from the KPNC Early Start screening are also used to identify opioid exposure during pregnancy.

- Study Cohorts

We will use the KPNC database to create a birth cohort from 2010-2023. To perform the retrospective matched analysis for the proposal we will generate a NOWS cohort from the birth cohort, and additional discrete NOWS cohorts based on management approaches and timing/durations/doses of exposures. In KPNC, during the proposed study period, infants with NOWS have been managed either using opioid replacement pharmacotherapy or non-pharmacological care. Starting in 2016, KPNC standardized the management approach for infants with NOWS, with a structured ESC approach that includes keeping the maternal/infant dyad together, maximizing non-pharmacologic interventions, avoiding over-stimulation, empowering families, and only treating with opioid replacement if after optimizing the above interventions, symptoms interfere with the ability to feed, sleep, and be consoled. Prior to 2016, there was no standardized approach to managing NOWS, and infants were managed at the discretion of individual physicians, with a reliance on opioid replacement to control withdrawal symptoms. We therefore divide infants with NOWS who were managed non-pharmacologically into two distinct cohorts: ***Pre-ESC*** are those born before 2016 who were managed non-pharmacologically and ***ESC*** are those who were born 2016 or later who were or are managed non-pharmacologically with a structured ESC approach. Among those infants with NOWS that receive opioid replacement therapy, they are divided into: ***Pre-ESC Rx*** are those born before 2016 and ***Post-ESC Rx*** are those born 2016 or later. In addition, we will have a "sustained exposure" cohort, an "early gestational exposure" cohort and a" high-dose exposure" cohort. The "sustained exposure" study cohort consists of those infants with NOW with durations of exposures for at least two four-week periods. The study cohort based on timing of gestational exposure consists of infants with NOWS either with prenatal opioid exposure during the third trimester only (late gestational), or with prenatal opioid exposures that occurred beginning in the first or second trimester of pregnancy (early gestational). The "high-dose exposure" cohort is restricted to infants with prenatal exposure to maternal prescription opioids. High dose is defined as having the cumulative dose in morphine milligram equivalents (MME) of prenatal opioid exposure in the top quartile of the entire group. We will also recruit a cohort using a subset of the birth cohort from 2013-2018 to perform prospective assessment as a pilot study.

- Outcomes

<u>In-hospital outcomes</u> are mortality, re-admission to hospital or NICU, NICU Length of Stay (LOS), hospital LOS, any surgical, diagnostic, or therapeutic procedures requiring sedation, respiratory support (oxygen therapy, CPAP, mechanical ventilation), need for medications for treatment of neurological symptoms and need for vasoactive medications for hemodynamic support.

<u>Neurodevelopmental outcomes</u> are assessed ***retrospectively*** by (1) diagnoses of disorders of cognition, development, behavior, and psychiatric conditions using ICD-9 or ICD-10 codes, (2) available EHR documentation of referral for evaluation for hearing, vision or autism spectrum disorders, language delay, physical, occupational therapy,

speech therapy or Individualized Educational Plan (IEP). Neurodevelopmental outcomes are assessed ***prospectively*** using (1) the home version of ADHD-Rating scale, fifth edition (ADHD-RS-5) to assess ADHD and (2) the Colorado learning difficulties questionnaire (CLDQ) to assess learning difficulties. We will also trial the use of additional validated neuropsychological (NIH Toolbox) and behavior instruments (ABAS II and Conner CBRS).

- Specific Aims

Aim 1A: To compare in-hospital and neurodevelopmental (ND) outcomes between infants with NOWS treated with opioid replacement and those managed non-pharmacologically, including using the "Eat, Sleep, Console" approach.
Aim 1B: To perform a pilot prospective cohort study to assess feasibility of comparing ND outcomes between non-pharmacologically managed and opioids replacement treated infants with NOWS.
Aim 2A: To characterize the sources (prescription versus illicit opioids) and doses (total milligram morphine equivalents) of opioid exposure and co-exposures to other substances in infants with NOWS.
Aim 2B: To examine the in-hospital and ND outcomes in infants with NOWS with high MME (milligram morphine equivalent) prenatal opioid exposure and compare the effects of management approach between high and other MME groups.
Aim 3A:To characterize the timing and duration of opioid exposure in infants with NOWS, and to compare the in-hospital and ND outcomes between infants with sustained and non-sustained exposure and between infants with and without early gestational exposure.
Aim 3B: To assess how varying duration or timing of prenatal opioid exposure modifies the effects of management approach on in-hospital and ND outcomes in infants with NOWS.

- Tasks, Milestones and Deliverables

The proposed project consists of <u>five tasks</u> to be completed over a four-year period:

Task 1 **Project Preparation & Planning**: query of the KPNC databases and other data sources to conduct the proposed research aims.
Task 2 **Testing and Selecting Models for Analysis**: testing of different matching models that results in selecting the variables and model for the matched analysis of the project.
Task 3 **Data Analysis**: Performing analyses for each of the three study aims.
Task 4 **Dissemination of Study Results**: through presentation at scientific meetings and submission of study findings for publication.
Task 5 **Project Monitoring and Team Communication**: meetings and reports

Timeline and Deliverables

	Year 1	Year 2	Year 3	Year 4	Deliverables
Task 1					All data elements (demographic, clinical, exposure & outcome) are identified, reviewed and finalized for the project.
Task 2					Identify and finalize match variables. Select best matching model after testing of multiple matching models.
Task 3					Obtain results from analysis of Aim1, Aim 2 and Aim 3. Additional analysis as indicated by guided by the findings
Task 4					Prepare results for presentations at scientific meetings. Publications of study results in peer-reviewed journals.
Task 5					Monthly investigator phone conferences and regularly held in-person investigators meetings. Monthly progress reports to FDA.

5. INTRODUCTION

5.a. Responses to reviewers' comments

The reviewers indicated there are several issues that were not addressed in the Whitepaper submitted for the proposed study. Please see our responses and action plans below.

1. *The study topic is a high priority area in regulatory science, however some of the study aims do not have a clear regulatory impact. We recommend reframing the study aims to focus on determining differences of non-pharmacologic (i.e., Eat-Sleep-Console) vs. pharmacologic treatment on NOWS outcomes.*

We have reorganized our specific aims to focus on determining the differences in the in-hospital and neurodevelopmental outcomes between the non-pharmacologically managed and pharmacologically treated infants with NOWS. In Aim 1, we will compare outcomes between non-pharmacologically managed and pharmacologic treatment in infants with NOWS. In Aim 2, we will examine the doses of opioid exposures and co-exposures to other substances as modifiers of effects of management approaches on outcomes. In Aim 3, we will examine timing and duration as modifiers of effects of

management approaches on outcomes.

2. *Retrospective studies are a useful option for gathering and evaluating data from a difficult-to-recruit and difficult-to-treat population. However, they have certain limitations and can introduce biases, such as in recordkeeping. To strengthen this proposal, we recommend re-scoping the study to add a small prospective cohort of cases to follow, based on the same criteria as retrospective data, and evaluate whether your findings from the retrospective studies can predict or inform treatment outcomes.*

In Aim 1B, we propose to conduct a pilot study and recruit a small number of infants with NOWS born between 2013-2019 and prospectively assess ND outcomes at ages 6-12 years. The results of the pilot study will support the planning of a full prospective cohort neurodevelopmental outcome study.

The budget in our Whitepaper does not include recruitment and assessment of a prospective cohort. Therefore, we are submitting a revised budget that includes the cost of a neuropsychologist consultant, IRB preparation, setup of a Redcap database, and incentives for study participants.

3. *In addition to including timing and duration as measures of exposure, consider adding dosage information as a predictive variable. Dosage may act as a moderating or mediating variable and could make the results difficult to interpret if not controlled for. In addition, explain how maternal dose of opioid analgesic prescriptions or medications for opioid use disorder (e.g., buprenorphine or methadone) would be treated in the exposed groups. The proposal identifies that concomitant exposure with controlled substances and psychotropic medications may be a confound. Explain how this potential confound will be addressed.*

We have revised the proposal to include examination of dosage of exposure on outcomes. In infants with NOWS who had prenatal exposure from prescription opioids we will have reliable data from pharmacy records to quantify maternal doses of opioids in total milligram morphine equivalents (MME). In infants with NOWS who had prescription opioid exposure, we will designate those with exposure at the top quartile of MME doses as the high MME group. We will further examine the comparative outcomes between management approaches in the high MME group and other MME groups. In the revised proposal, we will examine substances co-exposures including prescription psychoactive medications. Co-exposures will be adjusted for in the matched analysis, or using regression models after matching when matching does not control them sufficiently.

4. *Consider additional metrics for early neurodevelopmental outcomes. The listed outcomes for neurodevelopment may not be diagnosable until after age two. Earlier measures, such as qualification for Early Intervention services (e.g., speech therapy, physical therapy), may serve as earlier, clinically meaningful outcome variables.*

We have included additional metrics for early neurodevelopmental outcomes in the full proposal. Specifically, the metrics are evaluation for hearing, vision or autism spectrum disorders, language delay, referral for physical, occupational therapy, or speech therapy, as well as referral for individualized educational plan (IEP).

5. *In the full proposal, identify and provide a plan for filling specific support staff roles. The speed and quality of hires for data analysis, project management, and research assistance will impact the project timeline and its overall success. Additionally, include a description of study limitations, provide a brief description of the statistical analysis plan, such as power analysis and statistical test(s) for experimental goals involving hypothesis testing, and describe plans for study documentation.*

We have identified specific individuals who will be filling the support staff positions for data analysis, project management and research assistance. Their names and detailed responsibilities are included in the Cost Proposal budget and budget justification. Study limitations, and statistical analysis plan are included in the Full Proposal.

6. *Because FDA's funding is contingent on Congressional appropriations, it would be helpful to include an outline of one or more deliverables per each year of funding.*

We have included in the proposal specific deliverables for each year (see .8.1 Deliverables Schedule by Year)

5.b. Background

During the national opioid crisis, the tremendous increase in opioid use by pregnant women has resulted in an estimated seven-fold increase in infants born with neonatal opioid withdrawal syndrome (NOWS) due to prenatal opioid exposure[1, 2].

Several studies have shown that adverse neurodevelopmental outcomes occur in infants with NOWS from prenatal exposure to opioids [3, 4]. Infants with NOWS often have not only prenatal opioid exposure but also co-exposure to other substances[5, 6]. These substances include alcohol, cigarettes, cocaine, marijuana, amphetamines, selective serotonin uptake inhibitors [7] and other anti-depressant medications. Many, but not all, of these substances have been shown to have deleterious neurodevelopmental effects thus confounding the interpretation of the adverse effects of prenatal opioid exposure on ND outcome[8, 9]. Aside from the drugs of exposure, another area that deserves further investigation is the timing and duration of exposure. Most outcome studies in infants with NOWS have concentrated on exposures that occurred during the last 90 days before delivery, with very little data regarding outcomes in infants with prenatal exposures to opioids and/or other substances that occurred or began during early pregnancy or mid-pregnancy. Our proposal aims to examine the effects of timing and duration of exposure to opioids on in-hospital and ND outcomes, thus filling the current gap in knowledge.

Clinical signs of NOWS result from neurobiological dysregulation in control of sleep cycle, motor/muscle tone, autonomic functioning, and sensory processing. Management of NOWS aims to reduce the signs and symptoms of NOWS including pharmacotherapy with opioid replacement based on traditional Finnegan Neonatal Abstinence Scoring System (FNASS) or non-pharmacological strategies. While management of substance-exposed infants has always included nonpharmacologic care, there has been a recent transition from using FNASS to the Eat, Sleep, Console (ESC) function-based method for assessing symptoms to guide treatment of NOWS[2, 10-14], with a much greater reliance on non-pharmacological care for infants with NOWS. The principles of non-pharmacological ESC care include (1) minimizing environmental stimuli (both light and sound), (2) swaddling to reduce stimulation and promote sustained sleep, (3) responding early to infant agitation, (4) Kangaroo care and use of pacifiers, (5) preventing diaper dermatitis, (6) applying positioning and comforting techniques (swaying, rocking), (7) using music and massage therapy, (8) providing nutritional support including frequent and small feeds and use of high caloric feeds, and lower lactose formula, (9) promoting rooming-in of mother and infant, and (10) having active maternal participation, particularly encouraging breastfeeding if not contraindicated. In 2020, the American Academy of Pediatrics issued a guidance of clinical care that stated “nonpharmacologic interventions should be used for all infants with opioid exposure and should be considered the foundation of care” for NOWS and “pharmacologic therapy should be considered for severe opioid withdrawal”. However, the benefit in terms of outcomes using the ESC approach has not been consistently shown[2, 10-15]. Several studies have shown that ESC reduces the percentage of infants requiring pharmacotherapy and length of stay (LOS) compared to the FNASS. Other studies have not demonstrated such benefits. It has been suggested that treatment of dysregulation associated with NOWS with opioid replacement therapy may in fact be beneficial in minimizing long-term adverse neurodevelopment. To date, there have been no data on whether ESC could improve ND outcomes[2, 3, 10-15].

Outcome studies in infants with NOWS can provide important data for understanding potential health care resource utilization in the affected infants during infancy, childhood[16-19], and beyond. In a study using the Medicaid dataset from 2003 to 2013, children with neonatal abstinence syndrome (NAS) had more hospital admissions, emergency room visits, prescription medications, and outpatient encounters during the first three years of life compared to those without NAS[20]. With respect to comparative costs between different management approaches, several studies have provided evidence that in infants with NOWS, non-pharmacological management was associated with lower hospitalization costs as results of their having shorter hospital stays and there was a reduced need for pharmacological treatment[14, 21, 22]. However, since studies of late neurodevelopmental outcomes in infants with NOWS are still lacking[23], there are no data regarding long-term health care resource utilization between infants who are pharmacologically managed and those who are managed with ESC. Thus, studies of neurodevelopmental outcomes are urgently needed to guide public health planning and policy decision making.

6. STATEMENT OF WORK

This Statement of Work (SOW) is an indivisible single undertaking that cannot be divided into separable SOW units.

6.a. Scope

6.a.1. Goals: The scope of the proposal includes the following goals:

1) Generate a dataset using the Kaiser Permanente Northern California research databases, which combine administrative/billing data and clinical/pharmacy data from electronic health records (EHR), to create a birth cohort of all infants born between 1/1/2010-12/31/2023.
2) Create study cohorts from the birth cohort 2010-2023 to address each of the three aims:
    a. Infants with NOWS cohort (NOWS cohort): all infants evaluated or scored for abstinence symptoms)
        i. Retrospective
        ii. Prospective
    b. NOWS cohort by management approaches and birth years
        i. Non-pharmacological managed: Pre-ESC and ESC
        ii. Opioid replacement treated: Pre-ESC Rx and Post-ESC Rx
    c. NOWS cohort with only prescription opioid exposure
        i. High MME and other MME dose cohorts
    d. NOWS cohort according to duration or timing of exposure
        i. Sustained and non-sustained exposure cohorts
        ii. Late gestational and early gestational exposure cohorts
3) Examine outcomes
    a. In-hospital outcomes
    b. Neurodevelopmental outcomes identified by ICD-9 and/or ICD-10 diagnostic codes for disorders in development, cognition, behavior and neuropsychiatric conditions. Prospective assessment of ND outcomes.
4) Identify and test variables for matching that may be included in the multi-variate matched analysis:
    a. maternal data elements.
    b. infant data elements.
    c. exposure data elements.
    d. outcomes data elements.
5) Test models for matched analysis.
6) Finalize variables for the matched sets and finalize matching model.
7) Conduct multivariate matched analysis of in-hospital and neurodevelopmental outcomes comparing infants with NOWS who were non-pharmacologically managed (ESC) with those who were opioid replacement-treated.

6.a.2. Tasks: The project will consist of Five different Tasks (see details under ***d. Tasks and Subtasks*** below), each with specific deliverable(s).

1) Task 1: Project Preparation and Planning focuses on query of the KPNC databases and other data sources to conduct the proposed research aims. The deliverable of a final dataset that will be used for analysis.
2) Task 2: Pre-analysis Phase of the Project focuses on testing of different matching models that results in selecting the variables and model for the matched analysis of the project. The deliverable of the task is finalizing the model for the matched analysis.
3) Task 3: Project Analysis Phase consists of performing all of the analyses for each of the three study aims. Deliverables of this task are the analysis results of the three Aims.
4) Task 4: Results Dissemination includes preparation and presentation of study findings, drafting of manuscripts, and submission of study findings for publication. The deliverable of this task is the submission of the Final Report to the FDA.
5) Task 5: Project Monitoring and Team Communication. This task involves team communication and monitoring progress of the project and spans the entire project period. The deliverables include regular research team in-person meetings and monthly phone/video-conferencing calls with the research team. In addition, monthly Progress Report will be submitted to the FDA.

6.b. Objectives

The objectives of the proposed study are to examine the effects of postnatal management approaches (non-pharmacological, including ESC versus opioid replacement pharmacotherapy) and the timing and duration of gestational opioid exposure on in-hospital and neurodevelopmental outcomes in infants with NOWS.

6.c. Technical Approach

6.c.1. Study Design: The proposed study employs both retrospective and prospective cohort study design to test two hypotheses: (1) Structured approach in non-pharmacological management using “Eat, Sleep, Console” (ESC) improves in-hospital and ND outcomes in infants with NOWS. (2) Timing, doses and durations of prenatal opioid exposure are modifier of the effects of management approaches on in-hospital and neurodevelopmental outcomes.

6.c.2 Methods

6.c.2.1 Data Source: We will use the KPNC Virtual Data Warehouse (VDW) and several existing research databases/registries: the infant cohort (IC) dataset and the Neonatal Minimum Dataset (NMDS). The VDW contains membership, outpatient pharmacy, medical encounter, diagnostic, health service, and laboratory data extracted from the electronic health records (EHR) and additional mortality, census, and birth certificate data. The IC dataset contains all KPNC births with infant and mother demographic data, diagnostic codes for the maternal encounter & infant birth hospitalization, outcomes data on death, length of stay, NICU admission. The NMDS captures clinical information on interventions, diagnoses, outcomes of all infants admitted to NICU within KPNC through abstraction by chart reviewers using a

standardized abstraction protocol/definitions with electronic data capture from EHR.

6.c.2.2 Study Cohorts: The inclusion and exclusion criteria are summarized below

	Inclusion Criteria	Exclusion Criteria
Birth Cohort	• All infants born 2010-2023. • Follow-up data available after age 24 months.	• Delivery room deaths. • Chromosomal abnormalities • Congenital anomalies.
NOWS Infant Cohort	• Mother with the following during pregnancy: (1) Prescription for opioids (2) + urine tox screen for opioids (3) + for KPNC Early Start drug use survey • History of diagnosis of NOWS/NAS. • Evaluated, scored for abstinence after birth • P779.5, P96.1, P04.49 in 1st 7 days of life and received opioid replacement treatment or non-pharm management, e,g, ESC	No scoring (Finnegan) or evaluation documented for abstinence.
Retrospective NOWS Cohort	• NOWS cohort born 2010-2023	
Prospective NOWS Cohort	• NOWS cohort born 2013-2018 • parents consented for prospective assessment of the child at ages 6-12 years	• infants with NOWS not born between 2013-2018. • infants with NOWS unable to be recruited for study
MME Dose NOWS Cohort	• Source of opioid exposure is prescription opioids • Opioid exposure at top ¼ (high MME)	• Sources of opioid exposure other than prescription opioids • Insufficient data for MME
Sustained Exposure NOWS Cohort	• Opioid exposure for ≥ 2 four-week periods during pregnancy	• Opioid exposure < 2 four-week periods during pregnancy
Gestational Exposure NOWS Cohort	• Opioid exposure based on trimester of exposure • Late gestational exposure cohort: opioid exposure during the third trimester only. • Early gestational exposure cohort: initial opioid exposure during 1st and/or 2nd trimester	• Data for timing of exposure not available

Below is a summary of the Retrospective and Prospective NOWS study cohorts:

Retrospective, Sustained Exposure, Late Gestational Exposure and MME Dose NOWS Cohorts		
	Inclusion Criteria	**Exclusion Criteria**

Treated NOWS (Pre-ESC Rx)	• NOWS cohort born 2010-2015 • opioid replacement treatment	
Treated NOWS (Post-ESC Rx)	• NOWS cohort born 2016-2023 • opioid replacement treatment	
Non-Pharm Management (Pre-ESC)	• NOWS cohort born 2010-2015 • No opioids replacement treatment	Received pharmacotherapy to treat opioids withdrawal signs and symptoms.
Non-Pharm Management By ESC (ESC)	• NOWS cohort born 2016-2023 • No opioids pharmacotherapy • ESC approach management	Received pharmacotherapy to treat opioids withdrawal signs and symptoms.

Prospective NOWS Cohort		
	Inclusion Criteria	**Exclusion Criteria**
Treated NOWS (Pre-ESC Rx)	• NOWS cohort born 2013-2015 • opioid replacement treatment	
Treated NOWS (Post-ESC Rx)	• NOWS cohort born 2016-2018 • opioid replacement treatment	
Non-Pharm Management (Pre-ESC)	• NOWS cohort born 2013-2015 • Received only non-pharmacological management	Received pharmacotherapy to treat opioids withdrawal signs and symptoms.
Non-Pharm Management By ESC (ESC)	• NOWS cohort born 2016-2018 • Managed only using a structured ESC approach	Received pharmacotherapy to treat opioids withdrawal signs and symptoms.

6.c.2.3. Outcome Measures

Outcomes will include short-term in-hospital outcomes, and late neurodevelopmental outcomes that are both retrospectively and prospectively assessed.

In-hospital outcomes are mortality, re-admission to hospital or NICU, NICU Length of Stay (LOS), hospital LOS, any surgical, diagnostic, or therapeutic procedures requiring sedation, respiratory support (oxygen therapy, CPAP, mechanical ventilation), need for medications for treatment of neurological symptoms, need for medication for hemodynamic support. The primary outcome for in-hospital outcomes is a composite of having any one of the following: mortality, requirement for additional therapy or readmission to hospital or NICU.

Neurodevelopmental outcomes are assessed ***retrospectively*** by (1) diagnoses of disorders of cognition, development, behavior and psychiatric conditions using ICD-9 or ICD-10 codes, (2) available EHR documentation of referral for evaluation for hearing, vision or autism spectrum disorders, language delay, physical, occupational therapy, or speech therapy. Neurodevelopmental outcomes are also assessed ***prospectively*** using (1) the home version of ADHD-Rating scale, fifth edition (ADHD-RS-5) to assess ADHD and (2) the Colorado learning difficulties questionnaire (CLDQ) to assess learning difficulties.

The primary ND outcome is the presence of any of the following codes denoting an abnormal ND outcome in the retrospective analysis:

(1) Autism Spectrum Disorders: 299.0, 299.8, 299.9 (ICD-9), F84.0, F84.5, F84.8, F84.9 (ICD-10).
(2) Behavioral disorders: Attention Deficit Hyperactivity Disorders (ADHD): 314 (ICD-9), F90 (ICD-10), other Behavioral Disorders: 300, 312, 313 ((ICD-9), F91, F93, F94, F98 (ICD-10).
(3) Cognitive disorders: 317, 318, 319 (ICD-9), F70, F71, F72, F73, F78, F70, R41.83 (ICD-10)
(4) Developmental disorders: 315 (ICD-9), F80, F81, F82, F88, F89 (ICD-10)
(5) Depression, anxiety and other psychiatric disorders: 311 (ICD-9), F32, F33 (ICD-10)

The secondary ND outcomes (1) any documented referral for evaluation of delay in language development, speech or autism (2) documented referral for additional supportive therapy including occupational, Individualized Educational Plan (IEP) and (4) scores obtained from prospective assessment using ADHD-RS-5 or CLDQ.

6.c.2.4. General Matching Algorithms for Data Analysis

To construct matched comparisons between each exposure of interest and relevant controls, we will first determine the optimal matching ratio (i.e. the number of controls k to select for each exposed subject) by comparing sample sizes and propensity scores estimated using logistic regression. We will construct the matched groups using a two-step process[24]. First, a group of matched controls will be selected in the appropriate ratio (nk controls to n pharmacologically treated) to satisfy balance constraints on the pre-treatment variables, which will be chosen to ensure that the selected groups have distributions as similar as possible. If it is not possible to balance subjects adequately, the exposed subjects most dissimilar from the controls (e.g. in Aim 1A, pharmacologically treated subjects with severe symptoms) may be pruned for the sample, or weighting methods may be used to give more fine-grained control of balance[25]. Next, each pharmacologically treated subject will be paired with exactly k of the selected controls, producing n matched sets. This pairing will be conducted to maximize similarity on multivariate Mahalanobis distances, as well as similarity on propensity scores and individual variables important to the specific comparison. Matching will be conducted using the software packages designmatch and rcbalance in R[25-27]. Subgroup analyses will be conducted by enforcing exact agreement on the relevant subgroup variable in the second step to create pure subgroups for each level of the subgroup variable.

Outcome analysis for each matched comparison will be conducted by computing simple risk differences and by fitting conditional logit and stratified Cox proportional hazard models. Risk differences provide the most direct and interpretable results but do not correct for residual differences after matching or variable follow-up times. The logit and Cox models both allow adjustment for variables that cannot be balanced perfectly. They will be especially useful for possible co-exposure differences between pharmacologically treated subjects and controls that may be too large to be corrected

by matching. The Cox models will also be able to incorporate variable follow-up times due to large differences in length of surveillance across our multiyear cohort. When conducting subgroup analyses, interaction effects will be added to the logit and Cox models to allow for different estimates in distinct subgroups. Hypothesis tests will be conducted using within-match permutation tests and model-based estimates and confidence intervals will also be presented. Sensitivity analyses for unobserved confounding will be conducted, using the method of Rosenbaum[28] for risk differences and the method Lin, Psaty, and Kronmal [29]for logit and Cox models. We will also measure intensity of follow-up after exposure using data on completion of well-child visits, and if follow-up rates differ significantly after matching, we will conduct additional sensitivity analysis by adjusting for well-child visit status and its interaction with exposure in our model-based approaches.

6.c.3 Specific Aims

6.c.3.1 Aim 1A: To compare in-hospital and neurodevelopmental (ND) outcomes between infants with NOWS treated with opioid replacement and those managed non-pharmacologically, including using the "Eat, Sleep, Console" approach.

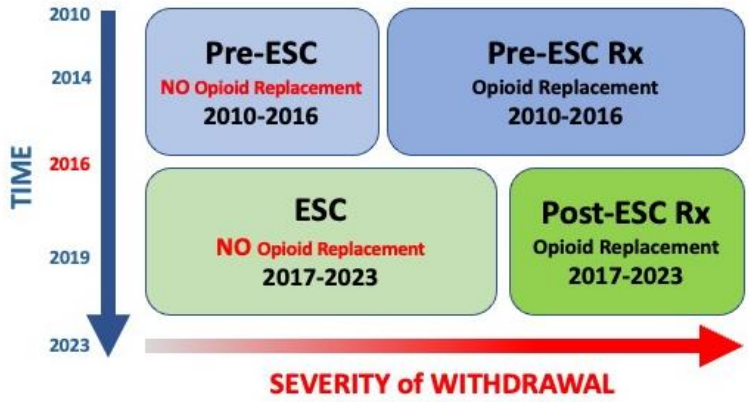
We will test the hypothesis that ***infants with neonatal opioid withdrawal syndrome (NOWS) experience improved in-hospital and neurodevelopmental (ND) outcomes when managed using a structured "Eat, Sleep Console" non-pharmacological approach compared to opioids replacement treatment***. We will use real-world data provided by the Kaiser research database to compare differences in outcomes between using this non-pharmacological approach and pharmacological opioids replacement in infants with NOWS. We will examine both short-term in-hospital outcomes and later neurodevelopmental outcomes.

Rationales: Finnegan scoring has been used traditionally to evaluate withdrawal symptoms among infants with NOWS in determining their need for opioid replacement pharmacotherapy. More recently, the use of ESC assessment tool has focused on function-based scoring for abstinence, prioritizing the use of non-pharmacological management. Several studies have shown that using scoring by the ESC assessment tool to determine the care administered to infants with NOWS improves LOS (length of stay); however, data on long term neurodevelopmental outcomes are lacking. Throughout the entire proposed study period, the standard of care in managing infants with NOWS in the Kaiser Permanente Northern California (KPNC) health system has always been to prioritize non-pharmacological approaches. In 2016, non-pharmacological management was formalized as a structured "Eat, Sleep, Console" approach at KPNC. Our proposal aims to compare non-pharmacological approaches in general, and the structured ESC approach in particular, with opioid replacement treatment in NOWS infants. Our study cohorts are organized based on management approaches and birth years.

- ***All Non-Pharm*** are all non-pharmacologically managed in the entire birth cohort.
- ***All Rx*** are all who received opioids pharmacotherapy in the entire birth cohort.

- ***Pre-ESC*** are those managed non-pharmacologically before the structured ESC approach was instituted in 2016.
- ***ESC*** are those managed using the structured ESC approach beginning 2016.
- ***Pre-ESC Rx*** are those managed with opioid replacement therapy before 2016
- ***Post-ESC Rx*** are those managed with opioids replacement therapy 2016 or later

Severity of withdrawal symptoms varies systematically across different study cohorts, and does so differently across birth years as depicted below:



Detailed Study Protocols: We will compare in-hospital and ND outcomes between the two different management approaches in infants with NOWS. First, infants with NOWS from the entire birth cohort (2010-23) will be used to compare outcomes between those non-pharmacologically managed with those treated with opioids replacement: ***All Non-Pharm vs All Rx***. We will also compare outcomes between the two management approaches used after implementation of the ESC approach in 2016: ***ESC vs Post-ESC Rx*** *(*ESC-managed vs opioids replacement treated infants with NOWS born after 2016).

Finally, we will compare outcomes between infants with NOWS managed using an ESC approach with those treated with opioids before 2016: ***ESC vs Pre-ESC Rx***. The 2016 implementation of a structured ESC approach may have lead providers to initiate opioid replacement therapy at higher levels of withdrawal symptom severity than they did before ESC. The Pre-ESC Rx group during the period of “usual care” as the comparative arm in the analysis will therefore address confounding by indication that might have occurred with the ESC implementation and better simulate a randomized comparison between ESC and opioid replacement therapy.

Preliminary Data: Total number of available children for each study cohort is shown:

	Pre-2016	**2016-2019***	**Total (2010-2019)**
NOWS infants	900	621	1521
Non-Pharm	(Pre-ESC) 751	(ESC) 486	1237
Opioids Rx	(Pre-ESC Rx) 149	(Post-ESC Rx) 135	284

*2020-2023 study cohorts will be added during the project study period.

Power analysis (All Rx vs. All Non-Pharmacological***):*** Power at a given sample size for detecting a given hazard ratio (HR) comparing all pharmacologically treated infants to non-pharmacologically managed infants is shown below.

# matched samples (% of total Rx treated cohort)	Hazard Ratio (HR)		
	1.7	1.8	1.9
300 (75%)	0.68	**0.78**	**0.85**
330 (83%)	0.72	**0.82**	**0.88**
360 (90%)	**0.76**	**0.85**	**0.91**
400 (100%)	**0.80**	**0.88**	**0.94**

The sample size given is the number of matched pairs chosen from each group (assuming 1:1 matching ratio). Sample sizes in the table range from 75%-100% of estimated total pharmacologically treated infants from 2010-2023, allowing for the possibility that some of these infants will be too dissimilar to the non-pharmacologically treated group to be matched. To carry out the power calculations, we used time-varying estimates of the incidence of any adverse neurodevelopmental event and of the rate of censoring in the portions of the non-pharmacologically managed cohort and the ESC cohort currently available from 2010-2019 KPNC data. We scaled up the current size of the pharmacologically treated sample (n=284) by 1.4 to account for the additional data we aim to collect in the four additional years (2020-2023). Power was computed using the function “powerCT.default” from the R package powerSurvEpi [30], which implements a procedure described in Rosner (section 14.12)[31]. This procedure is designed for grouped Cox models rather than the paired Cox models we intend to fit, which will account for additional data adjustments via matching.

6.c.3.2 Aim 1B: To perform a pilot prospective cohort study to assess feasibility of comparing ND outcomes between non-pharmacologically managed and opioids replacement treated infants with NOWS.

Rationale: With many of the limitations of retrospective analysis, the strength of evidence regarding ND outcomes will be greatly enhanced if the longitudinal prospective cohort study can be conducted on the Kaiser birth cohort. A prospective cohort study will directly assess ND outcomes with focuses in specific domains, which cannot be done using the current data source.

We propose to perform a pilot study that will determine the feasibility of performing prospective assessment of ND outcomes in our study cohorts. We will recruit infants with NOWS from the 2013-18 birth cohort to determine our ability to contact, recruit, enroll and prospectively assess study participants at ages 6-12 years. The age range of 6-12 years captures school age, when issues of learning, language, attention and behavior will be most important. This age range also allows for direct assessment of study participants, in addition to parental or self-reporting using validated assessment tools. We selected the cohort to span the birth years 2013-18 to cover an equal period before and after the implementation of ESC in 2016. By ending birth year in 2018 for the

cohort, we will also avoid any confounding from concerns related to the COVID-19 pandemic. The pilot study will provide useful data for power analysis for sample size for a larger prospective cohort study. In addition, comparing results from the prospective assessment and those from the retrospective analysis have the potential to inform what retrospective data source are most reliable, thus improving the design of future studies.
Preliminary Data: Total number of available study children for each cohort is shown:

	Pre-2016 (2013-2015)	**2016-2018**	**Total (2013-2018)**
NOWS infants	508	480	988
Non-Pharm	(Pre-ESC) 415	(ESC) 342	787
Opioids Rx	(Pre-ESC Rx) 93	(Post-ESC Rx) 108	201

Detailed Study Protocols: In the prospective NOWS cohort pilot study, we will recruit 10 children from each of the following four cohorts: Pre-ESC, ESC, Pre-ESC Rx and Post-ESC Rx. We will use the data collected to design a prospective cohort study to compare ND outcomes between infants with NOWS managed by an ESC approach with those who receive opioid replacement therapy. We will work with study participants' primary pediatricians to obtain contact information for study participants. A member of the research team will contact the family by email, phone and mail for recruitment into the study. We will obtain informed consent from those eligible for the study and agree to participate. Enrollled children will complete a review of medical and surgical history, including hospitalizations and medications, and verify recorded demographic data. Parent(s) or caretakers will be asked to complete (1) an ADHD assessment using the home version of the ADHD-Rating scale, fifth edition (ADHD-RS-5) and (2) a learning difficulty assessment using the Colorado learning difficulties questionnaire (CLDQ). We will additionally administer a questionnaire regarding home environment. We will explore with a subset of the enrolled study participants to participate in in-person assessments using ABAS II, *Conners* CBRS Comprehensive Behavior *Rating* Scale (parent and self-report) and the NIH Toolbox. Study participants will be invited to have the in-person sessions when contacted for the questionnaires. Study participants will be reimbursed $100 per encounter for their time to complete an interview regarding medical history, CLDQ, ADHD-RS-5 or home environment questionnaire or an in-person assessment session for ABAS II, Conners CBRS or NIH Toolbox.

We will document (1) the total number of children contacted, (2) eligible, (3) successfully consented, (4) enrolled, (5) with complete historical EHR data, (6) who successfully completed the two assessments and home environment questionnaire, and (7) agreed to participate in an in-person session and (8) completed an in-person session. Results from the retrospective analysis will be retrieved and compared with those obtained from prospective assessments. A draft data collection form will be developed, which will include demographic data, all retrospective collected data, and data derived from the home environment questionnaire and prospective assessment results. The data collection form will be finalized and be used for the planned full prospective study. The results of the prospective assessment will be used to perform sample size estimation for the full prospective cohort study. We will also make plans to submit an IRB research proposal for the full prospective cohort study.

6.c.3.3 Aim 2A: To characterize the sources (prescription versus illicit opioids) and doses (total milligram morphine equivalents) of opioid exposure and co-exposures to other substances in infants with NOWS.

We will query the entire database to collect data regarding sources of prenatal opioid exposure (prescription opioids or maintenance therapy for addiction, other sources). We will query pharmacy records to determine the types of co-exposure substances or medications. We will specifically determine co-exposures to prescription medications for depression, anxiety and other DSM-5 conditions. To examine doses of prenatal opioid exposure, we will restrict examination to those study participants with prenatal exposure to prescription opioids, quantified in milligrams morphine equivalents (MME). We will specifically test the hypothesis that ***prenatal prescription opioid exposure at high MME is more frequently associated with co-exposure to other prescription psychoactive medications.***

Rationales: Studies in infants with NOWS have mostly examined prenatal exposures to the opioids methadone, buprenorphine, or other illicit substances, with fewer studies examining exposure to prescription opioids[32]. The objective of Aim 2A is to characterize, in infants with NOWS, variation in sources (prescriptions, maintenance treatment for substances), doses (in milligrams morphine equivalents or MME), and psychoactive substances of co-exposure, including prescription anti-depressant and psychotherapeutic drugs. Our preliminary data indicate that the majority of prenatal opioid exposures in infants with NOWS from KPNC dataset derives from prescription opioids. The pharmacy record also provides reliable data on doses of prescription opioids and types and doses of prescription antidepressants and psychoactive medications. We will therefore focus the examination of doses of opioid exposure in the group with prenatal exposure to prescription opioids, and co-exposures to prescription medications.

Detailed Study Protocols: In each of the NOWS study cohorts from Aim 1A, we will determine distribution of various sources of exposures: (1) prescription opioids, (2) maintenance treatment for addiction with methadone or buprenorphine, and (3) heroin and other illicit opioids. We will categorize co-exposure substances as follows: (1) amphetamines, (2) barbiturates, (3) other non-opioid substances, (4) prescription SSRI antidepressants, and (5) prescription non-SSRI psychoactive medications. We will characterize the relative frequency, categories, and total number of substances for each source of exposure.

To characterize doses of prescription opioid exposure, we will determine total cumulative doses in MME, and generate descriptive statistics for dosage (range, mean, median, and distribution) in each of the NOWS study cohorts. Doses of MME opioids will be divided into quartiles, and **the top quartile is the high MME dose**. We will create a high MME exposure cohort as those with prenatal prescription opioid exposure in the top quartile of dose by MME.

In the NOWS group with prenatal prescription opioid exposure, we will query the EHR to identify any documented maternal psychiatric diagnoses, defined as ICD-10-CM codes corresponding to a condition found in the DSM-V. We will also query the pharmacy record to obtain data on any prescription medications used to treat those conditions. We will examine the incidence of co-exposure, types of substances of co-exposure, and number of different co-exposure substances in the high MME group and the other MME (non-high MME) groups. We will further specifically determine in the high MME group incidence of co-exposure to SSRIs and other prescription psychoactive medications. Associations between MME and co-exposure will be tested using permutation methods for 2xk tables. The high MME and non-high MME NOWS cohorts created in Aim 2A will be used to perform matched analysis to examine the effects of doses on outcomes in Aim 2B.

Preliminary Data Among the entire NOWS cohort from 2010-2019, 926 (61%) had prenatal exposure to prescription opioids, 525 (34%) were exposed to methadone/buprenorphine and 80 (5%) had prenatal exposure to heroin. Co-exposure of the following substances: amphetamines, barbiturates, cocaine, THC, benzodiazepines, antidepressants, ETOH in NOWS cohort is presented below:

Sources of Prenatal Opioids	No co-exposure	+ Co-exposure
Heroin (n=80)	11%	89%
Methadone/Buprenorphine (n=515)	46%	54%
Prescription opioids (n=926)	47%	53%

6.c.3.4 Aim 2B: To examine the in-hospital and ND outcomes in infants with NOWS with high MME (milligram morphine equivalent) prenatal opioid exposure and compare the effects of management approach between high and other MME groups.

We will use the high MME cohort created in Aim 2A to the hypothesis that ***infants with NOWS who have high doses of prenatal prescription opioid exposure are at risk for worse in-hospital and ND outcomes***.

Rationales: Little is known regarding the relationship between dose, timing and duration of prenatal opioid exposure and neonatal outcomes, particularly long-term neurodevelopmental outcomes. Mothers with more serious substance use disorder or other co-morbid conditions may also have higher doses of exposure, so a dose-response curve between exposure and outcome needs to control for confounding introduced by co-morbidity and sources of prenatal opioid exposure. Our proposal will analyze dose-response effects using NOWS infants with prenatal prescription opioid exposure. Restricting this study to NOWS infants with a single type of opioid exposure minimizes some of the potential confounding of exposure to MAT or illicit drugs. In addition, the availability of detailed pharmacy records provides reliable quantitative data on doses of opioid exposure. Similarly, the KPNC dataset provides data regarding detailed timing of opioid use during pregnancy from EHR without relying on recall or self-report by mothers.

Detailed Study Protocols: We will first perform matched analyses to compare in-hospital and ND outcomes between the high MME group and non-high MME groups to test the hypothesis that high doses of prenatal opioid exposure increase risk for worse in-hospital and ND outcomes. We will match the co-exposure variables (types, and number) between groups in the match analysis. If the co-exposure variables are significantly imbalanced between groups such that adequate matching is not achievable, our alternative approach will be to perform the analysis with co-exposure variables in a regression model.

If the results indicate that the high MME group has worse outcomes compared to the other MME group, we will perform additional subgroup analysis to examine effects of management approach on outcomes in the high MME group. Specifically, we will perform subgroup analyses for the proposed comparison from Aim 1A (All Non-Pharm vs. All Rx) in high MME and all non-high MME groups. Should sample sizes permit, we will perform additional subgroup analyses for the other proposed comparison from Aim 1A (ESC vs. Pre-ESC Rx and ESC vs Post-ESC Rx)

6.c.3.5 Aim 3A: To characterize the timing and durations of opioid exposure in infants with NOWS, and to compare the in-hospital and ND outcomes between infants with sustained and non-sustained exposure and between infants with and without early gestational exposure.

We will test the hypothesis that ***infants with NOWS with long durations (sustained exposure) or with early gestational prenatal exposure are at risk for worse in-hospital and ND outcomes than infants who do not experience sustained exposure or early gestational prenatal exposure***. In the NOWS cohort, we will create sustained and non-sustained exposure cohorts based on the duration of exposure. We will create from the NOWS cohort two cohorts determined by the timing of exposure, one with and one without early gestational opioid exposure.

Rationales: A recent study using the MoBa cohort found that a longer duration of prenatal analgesic opioid exposure (> 5 weeks compared to ≤ 4 weeks) increases risk for diagnosis of ADHD[33]. Their use of a 4-week period for exposure has been used elsewhere and is our rationale for generating the sustained exposure cohort using multiples of 4-week periods. Using claims data from Optum, Wen et al. [34]found no association between opioid exposure and neurodevelopmental disorders, but increased risk was observed with longer duration or higher doses of opioid exposures. In the MoBa study, timing of exposure was not associated with increased risk for ADHD. Our proposed study will examine timing and duration of opioid exposure on broader neurodevelopmental outcomes as well as in-hospital outcomes, and whether these factors modify the effect of management approaches on outcomes.

Detailed Study Protocols: Duration of exposure will be quantified based on number of four-week periods of exposure. We will create a sustained exposure cohort consisting of NOWS infants with prenatal opioid exposures for 2 or more four-week

periods and a non-sustained exposure cohort with 2 or fewer four-week periods of exposure. We will perform matched analyses to compare in-hospital and ND outcomes between sustained and non-sustained exposure cohorts to determine if duration of exposure influences outcome.
Timing of exposure will be categorized by the first trimester in which the infant was exposed to opioids: first (0-12 weeks gestation), second (13-28 weeks gestation) and third (29 weeks till delivery). To examine the effects of timing of exposure on outcomes, we will create a late gestational exposure cohort consisting of infants with NOWS whose prenatal opioid exposure occurred ONLY during the third trimester and an early gestational exposure cohort consisting of infants with NOWS whose prenatal opioid exposure occurred initially during the first and/or second trimester. To determine whether timing of exposure affects outcomes, we will conduct matched analyses to compare in-hospital and ND outcomes between the late gestational exposure cohort with the early gestational exposure cohort.

6.c.3.6 Aim 3B: To assess how varying duration or timing of prenatal opioid exposure modifies the effects of management approach on in-hospital and ND outcomes in infants with NOWS.

We will test the hypothesis that ***timing and duration of prenatal opioid exposure could modify the effects of management approach on in-hospital and ND outcomes in NOWS infants.***

Rationales: Longer durations of exposure have been reported to be associated with increased risk of neurodevelopmental disorders, but no data exist regarding short duration of exposure on ND outcomes, and data related to timing on ND outcomes have been inconsistent. Any data available on whether timing or duration of prenatal exposure modify the effect of management approach on outcomes will be extremely helpful in guiding allocation of resources to specific vulnerable groups of NOWS infants, either with prolonged exposure or specific timing of exposure with NOWS, either with prolonged exposure or specific timing of exposure.

Detailed Study Protocols: We will compare in-hospital and ND outcomes between the two management approaches in the sustained and the non-sustained exposure cohorts by performing subgroup analyses for the sustained and non-sustained groups within the matched comparison of All Non-Pharm with All Rx constructed for Aim 1A. If we detect differences in outcomes between All Non-Pharm and All Rx only in the sustained exposure cohort, then the results would indicate that duration of prenatal opioid exposure may modify the effects of management approach on outcomes. Additional analyses to be performed will be guided by these results.

We will use the late gestational exposure and early gestational exposure cohorts to determine if timing of prenatal opioid exposure modifies the effects of management approach on outcomes. We will perform subgroup analyses for the matched comparison in Aim 1A, All Non-Pharm with All Rx, within the late gestational exposure and the early gestational exposure groups. If we find differences in outcomes between

All Non-Pharm and All Rx in only the early gestational exposure or the late gestational exposure group, then the results would indicate that timing of prenatal opioid exposure may modify the effects of management approach on outcomes. Additional analyses to be performed will be guided by these results.

6.c.4 Anticipated Study Results and Limitations

At KPNC, the structured ESC approach to management of NOWS was formalized at the end of 2015, and fully implemented by 2016. Our proposal aims to compare non-pharmacological management of NOWS, specifically the structured ESC approach, with opioids replacement treatment, for both short-term in-hospital outcomes and long-term ND outcomes. We recognize that evaluation of withdrawal symptom severity using the ESC assessment tool only began in 2020; our study is not comparing management approaches relying on tools used to assess severity of withdrawal symptoms but rather, comparing the use of non-pharmacological approaches with pharmacotherapy. We have previously reported that there are no differences between using the ESC tool and modified Finnegan scoring on initiation of pharmacotherapy. Thus, the KPNC NOWS cohort is an ideal cohort to compare outcomes between non-pharmacological approach and pharmacotherapy.

In the examination of timing and duration of prenatal opioid exposure as modifiers of the effect of management approach on outcomes, we propose to perform subgroup analyses within the sustained/non-sustained exposure cohorts, as well as the late/early gestational exposure cohorts comparing All Non-Pharm with All Rx. We will explore the possibility to also perform subgroup analyses comparing ESC with Pre-ESC Rx, and ESC with Post-ESC Rx, but these subgroup analyses are not included due to concerns related to limitations in sample sizes for the sustained/non-sustained exposure and late/early gestational exposure cohorts.

6.c.5 Clinical Guideline for Management of Neonatal Abstinence Syndrome at KPNC

Antenatal Management. The mothers of many of the babies evaluated and treated for NAS in KP nurseries are followed prenatally by the Early Start Program. Efforts should be made at each medical center to arrange prenatal counseling with the Neonatology or Pediatric HBS physicians who staff the nursery in the facility where delivery is planned. We recommend consultation for any mother on methadone or buprenorphine and any mother on daily opioids in the third trimester. A successful approach to arranging consultations utilizes a shared Healthconnect mailbox for the neonatologists or pediatricians to which consult requests can be sent by obstetricians or Early Start counselors. The counseling appointments may be in person but will typically be by phone and will enable the pediatric staff to introduce more detailed information about hospital workflows related to monitoring babies for evidence of NAS. Basic information about NAS scoring and anticipated length of stay should be included in the conversation. This is also an opportunity to inform the mother that the reason for monitoring and treatment of the baby will have to be shared with her partner and a plan to inform the partner in advance of the baby's birth is desirable. A smart phrase (.NASconsult) is available for providers doing phone consultations with families of

infants at risk for NAS. A KP Parent NAS Information Handout (revised 2018) is available and should be given to families in the third trimester.

Coding Recommendations. For an infant being observed in mother baby unit due to maternal exposure please use ICD-10 code P0449 "Newborn affected by maternal use of drugs of addiction". For infants requiring pharmacologic treatment, use code P961 Neonatal withdrawal symptoms from maternal use of drugs of addiction or code P96.2 Neonatal drug withdrawal syndrome maternal therapeutic drug.

Non-Pharmacological Management. There is mounting evidence that optimization of the hospital environment expedites weaning and discontinuation of opioid medications with the goal of discharge home (Bagley, 2014). The noise and disruption of open ward style NICU's is over-stimulating to infants suffering from NAS and appears to lead to increased duration of opioid weaning. Whenever possible, strategies should be implemented to move babies into private rooms where much of the care can be provided by the mother and other family members. For mothers who are compliant with a drug treatment program the standard recommendation should be to breast feed the baby. Breast milk provides optimal nutritional support and promotes mother-infant bonding. There is evidence suggesting breastfed neonates exposed to opioid maintenance treatment (OMT) medication prenatally have lower incidence of NAS and require shorter pharmacotherapy for NAS than infants who are not breastfed.

The following should all be addressed as part of a comprehensive NAS treatment program that should begin at birth, and not only when the baby shows signs of withdrawal. In a patient being observed/treated for NAS, use of the following measures should be reinforced: (1) Minimize environmental stimuli (both light and sound), (2) Swaddling lessens stimulation and promotes sleep that is more sustained, (3) Attempt to respond early to infant signals before agitation becomes amplified, (4) Kangaroo care and pacifiers may help to calm infants, (5) Prevent diaper dermatitis with application of petrolatum-based ointments &/or skin barriers containing zinc oxide with every diaper change. Follow the AWHONN Neonatal Skin Care Guidelines for additional prevention and treatment recommendations, (6) Teach and institute appropriate positioning and comforting techniques (swaying, rocking), (7) Music therapy and massage therapy may soothe some infants, (8) Frequent small volumes of feeds to allow adequate growth. For babies with excessive weight loss, which can be seen in the first 1-2 weeks of NAS care, fortification of breast milk to 22kcal/oz may be appropriate (caloric need maybe as high as 150-250 kcal/k/day), (9) Consider a partially hydrolyzed lower lactose formula for infants with diarrhea that is difficult to manage, (10) Promote rooming-in of mother and infant while assessing for NAS treatment. For those infants who require treatment, once drug tapering is initiated, move patient to a private room on the pediatrics floor if available in the facility, (11) Active maternal participation is the best non pharmacologic care. It is promoted by encouraging breastfeeding for mothers who adhere to a drug treatment program.

Finnegan Scoring. Most physicians and nurses who manage NAS utilize the Finnegan scoring system to identify babies who require therapy, and once on therapy to wean the treatment drug. Inter-observer variation in score assignment makes the use of the Finnegan scale problematic. This is particularly true as babies reach several weeks of age. There is some evidence that the normal score rises over the first month of life. Even with these limitations, we continue to recommend Finnegan scoring at this time.

(1) Start Finnegan scoring every 3-4 hours when a newborn is 12 hours of age. There is no clearly defined maternal opioid intake below which a fetus is not at risk for NAS. If there is a question about need for observation in the setting of low dose maternal opioid use, a neonatology or addiction medicine consult may be considered.
(2) Scoring should be done in the mother's room on the maternity ward, preferably while the baby is being held after a feeding. Babies at risk for NAS should be observed and scored in the hospital until 3-5 days of age before discharge home.
(3) For babies with scores >10: confirm nonpharmacologic measures are in place; add pharmacologic measures if nonpharmacologic measures are not sufficient to keep score ≤ 10
(4) For babies with any score >14, notify provider of the need to assess the baby.
(5) Finnegan scores tend to increase as infants mature over the first several weeks of life. In the third week of life, consider increasing the threshold from 10 to 12.
(6) See recommendations below for use of Finnegan scores for medication tapering.
(7) See attached appendix for definitions of specific components of the Finnegan Score.

Optimal Drug Therapy. For infants with severe opioid withdrawal, the mainstay of therapy is prescribing a replacement opioid to capture withdrawal symptoms, a short period of stabilization and a controlled taper of the replacement medication. Use of Tincture of opium is not recommended due to high alcohol content. Barbiturates should be avoided in the management of NAS because of long term neurodevelopmental concerns and availability of alternative, safer medications. After review of the available literature, we recommend the use of methadone. The long drug half-life in neonates permits every 12 hour dosing. Methadone also provides control of autonomic symptoms. Methadone at high dose may prolong the QTc interval. If the family history is positive for prolonged QTc an ECG should be obtained on the patient. Clonidine should be used in an adjuvant role when NAS is not controlled by methadone alone. The recommended approach to treatment is as follows: (1) Obtain a urine toxicology screen on all babies being evaluated for possible NAS. The presence of drugs other than opioids may complicate and prolong therapy, (2) Consider initiation of the methadone dosing schedule (see below) at step 1 for infants with two Finnegan scores greater than 10 or one greater than 1

Initiation and Escalation

Step 1: 0.1 mg/kg/dose orally every 6 hours for 4 doses

If the infant fails step 1 (score of greater than 10), consider steps 1A through 1C. Also, for babies who fail step 1, consider initiation of Clonidine (see below for dosing). After completing steps 1A through 1C, resume protocol at step 2. **Step 1A:** 0.1 mg/kg dose orally every 4 hours for 6 doses. **Step 1B:** 0.1 mg/kg orally every 8 hours for 3 doses. **Step 1C:** 0.1 mg/kg orally every 12 hours for 2 doses

Once stabilized, wean according to the following schedule

Wean to the next step if the average Finnegan score is less than 10 for prior 24 hours

If Finnegan score > 10, consider rescue dose of morphine 0.05 mg/kg dose orally

If infant requires more than 1 rescue morphine dose, return to dose in previous step of dosing schedule

Step 2: 0.07 mg/kg orally every 12 hours for 2 doses

Step 3: 0.05 mg/kg orally every 12 hours for 2 doses

Step 4: 0.04 mg/kg orally every 12 hours for 2 doses

Step 5: 0.03 mg/kg orally every 12 hours for 2 doses
Step 6: 0.02 mg/kg orally every 12 hours for 2 doses*
Step 7: 0.01 mg/kg orally every 12 hours for 2 doses*
Step 8: 0.01 mg/kg orally every 24 hours for 1 dose*
*When ordering the lowest doses in KPHC for small babies, it may be necessary to enter an explicit mg amount rather than a weight based dose.
Adjunct Consider adding clonidine if patient fails Step 1 methadone therapy and requires escalation to step 1A. (.i.e. if scores >10 after completion of step 1 above.) This may include babies with poly substance exposure or those whose methadone dose requires escalation to 0.1mg/kg/dose EVERY 4 HOURS with persistent elevation of Finnegan scores. (>10).

- Start clonidine at 1.5mcg/kg/dose orally every 6 hours
- Wean the patient off methadone as described above. The following day, wean clonidine to 50% of dose day 1, 25% of dose day 2, then off.
- Consider more frequent BP's during initiation and weaning of clonidine. Delay discharge for 1-2 days after clonidine is discontinued.

Discharge Observe for 36-48 hours from the last dose of step 8 if methadone is the only treatment agent. Consider adequate weight gain as a discharge criterion since weight gain may be a proxy for withdrawal severity. For infants with difficult to manage NAS who reach the high end of the dosing range for both methadone and clonidine, consider placing an Econsult for Addiction Medicine. In NCAL phone consultation is also available by calling 510 368 4504. Consultations are available during weekdays, weekends, and after hours. For any infants requiring pharmacologic treatment for NAS, there is evidence of increased risk of learning disability suggesting need for school age intervention. The benefit of High Risk Infant Follow up is unclear.

6.c.6 NASS (Modified Finnegan) Scoring Criteria (score in parenthesis)

- Excessive Crying: Unable to decrease crying within 15 seconds of self-consoling, or up to 5 minutes with caregiver interventions. (2)
- Continuous Crying: Unable to decrease crying within 15 seconds of self-consoling, or for longer than 5 minutes with caregiver interventions. (3)
- Sleep: Base on the longest period of sleep between scoring.
- Tremors: Mild= hands / feet only (1)
  Moderate = arm / leg (2)
  Undisturbed =wait 45 seconds after disturbing infant to see if tremors continue. If yes, then the tremors are undisturbed. (3 or 4 for mild or moderate)
- Increased Muscle Tone: Body rigidity or no head lag. Test while infant is quiet and awake - not sleeping or crying. (2)
- Excoriation: Do not assess for excoriation on buttocks related to loose stools. Assess for excoriation on nose, chin, cheeks, elbows, toes, etc. (1)
- Excessive Sucking: More than 3 attempts between scoring to self-console by sucking on pacifier, hand, fist, or other object. (1)
- Poor Feeding: Gulping, out of breath, uncoordinated feeding. (2)
- Loose Stool: Curdy, seedy, liquid without a water ring. (2)

• Watery Stool:	Liquid with a water ring. (3)
• Yawning/Sneezing:	3-4 yawns, 3-4 sneezes since last scoring. They do not need to be consecutive. Enlist help of parents and other caregivers to record events on log. (1 for yawning, 1 for sneezing).

6.c.7 References

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6.d Tasks and Sub-Tasks

Tasks				
Task 1: Project Planning and Preparation				
	Subtasks		Deliverables	Assessment Deemed Acceptable if
	1.1	Create NOWS cohort from birth cohort	Based on inclusion and exclusion criteria, NOWS cohort created from birth cohort 2010-2023.	NOWS cohort created.
	1.2	Query dataset for maternal exposures	Sources of maternal opioid exposure established	All data or sources of opioid exposure for the study cohorts are completed, and accuracy confirmed with select samples chosen from EHR for review and validation.
	1.3	Query pharmacy records for maternal exposures	Maternal opioid exposure re: timing during pregnancy, durations, types of opioids and doses established. Milligrams morphine equivalent doses of prescription opioids during pregnancy calculated.	Prescription opioids doses data are abstracted, and conversion to MME completed.
	1.4	Query dataset for postnatal management	Postnatal management by non-pharmacologic or opioids replacement treatment confirmed	Study cohorts created based on postnatal management with non-pharmacological approach or by pharmacotherapy.
	1.5	Obtain IEP and other developmental data	All referrals for evaluations of hearing, autism, speech identified. All referrals for occupational, physical and speech therapy identified. IEP referral data obtained.	All data related to referral for evaluations or supportive therapy are complete.
	1.6	Create study cohorts	Four different study cohorts from the NOWS cohort are created based on management approaches and birth years: Pre-ESC, ESC, Pre-ESC Rx and	Creation of study cohort based on management approaches and birth years is complete.

			Post-ESC Rx.	
Task 2: Testing and Selecting Models for Analysis				
	Subtasks		Deliverables	Assessment Deemed Acceptable if
	2.1	Generate and test match models	Generate and test different models for the matched analysis. Findings from the testing are summarized, with strengths and weaknesses of the different models identified.	Matching variables and models testing generate final list of variables and model for matching.
	2.2	Select match model to use for analysis	Select final model used for match analysis	Final model used for match analysis is selected
Task 3: Data Analysis of All Study Aims				
	Subtasks		Deliverables	Assessment Deemed Acceptable if
	3.1.1	Analysis Aim 1A All Non-Pharm vs All Rx	Analysis in the NOWS cohort, derived from the entire birth cohort from 2010-2023. Completed analysis with results that either show no differences or a difference in outcomes between non-pharmacological management compared to opioids replacement pharmacotherapy.	Analysis completed, and results regarding comparative outcomes between management approaches are found.
	3.1.2	Analysis Aim 1A ESC vs Pre-ESC Rx	Analysis that compares the in-hosp outcomes and ND outcomes between ESC-managed and opioids replacement treated infants with NOWS before 2016.	Analysis completed with findings reported.
	3.1.3	Analysis Aim 1A ESC vs Post-ESC Rx	Analysis that compares the in-hosp outcomes and ND outcomes between ESC-managed and opioids replacement treated.	Analysis completed with findings reported.
	3.2.1	Analysis Aim 1B Pilot prospective study I: Recruit/enroll	Contact children from each of the four cohorts: Pre-ESC, ESC, Pre-ESC Rx and Post-ESC to discuss study, and recruit study participants, and consent parents	Complete enrollment of 10 children from each of the four groups

	3.2.2	Analysis Aim 1B Pilot prospective study II.	Testing administered to the study participants. Draft data collection form.	Successfully complete testing in >80% of enrolled study participants.
	3.3.1	Analysis Aim 2A Sources, doses in NOWS cohorts	Determine the sources of opioid exposure in the entire NOWS cohort, and the four study cohorts.	Sources of exposure determined for all study cohorts. Analysis of doses in MME completed for prescription opioids exposed group. High MME cohort established and available for use in analysis.
	3.3.2	Analysis Aim 2A Co-exposures in NOWS cohorts	Characterize co-exposures in the NOWS cohort, the four study cohorts. Co-exposures include other substances (amphetamines, barbiturates, and illicit substances) and prescription psychoactive medications and SSRI	Co-exposures determined for all study cohorts. Co-exposures to prescription psychoactive medications determined,
	3.3.3	Analysis Aim 2A: Create MME cohort	In the group with prenatal prescription opioids, review of pharmacy records to determine doses (in MME): total cumulative, range, mean, median. The top quartile MME is denoted as the high MME cohort. Characterize co-exposures in the high MME cohort. Analysis of co-exposure to prescription psychoactive medications in the high MME group.	High MME dose cohort created. Analysis of co-exposure to prescription psychoactive medications in high MME group completed
	3.4.1	Analysis Aim 2B: Outcomes in high MME cohort	Compare In-hospital and ND outcomes between high MME group with the remaining MME (non-high) group.	Analysis completed with findings confirmed and available to be reported.
	3.4.2	Analysis Aim 2B: MME doses as a modifier of management approach	Subgroup analysis within the high MME and non-high MME groups comparing between different management approaches (All non-pharm vs All Rx).	Subgroup analysis completed with findings confirmed and available to be reported.
	3.5.1	Analysis Aim 3A	Determine the durations of exposures (in	Durations of exposures determined for

		Durations of exposures	weeks) in the NOWS cohort. Determine the distribution of exposure durations based on number of four-week periods in the NOWS cohort and the study cohorts	the NOWS cohort, including distribution for all study cohorts.
	3.5.1	Analysis Aim 3A Create sustained exposure cohort	Denote sustained exposure cohort: ≥ 2 four-week periods. All others are non-sustained exposure cohort.	Sustained exposure cohort created.
	3.5.2	Analysis Aim 3A Timing of exposures	Examine the timing of exposures based on the trimester(s) of exposure. Define distribution of gestational exposure in all cohorts.	Timing of exposure established and results available to be used for analysis.
	3.5.2	Analysis Aim 3A Create exposure cohorts based on timing	Designate infants with NOWS having exposure during the third trimester as the late gestational exposure cohort. Those with exposure that began in 1st and/or 2nd trimesters as the early gestational exposure cohort.	Exposure cohorts created based on timing of exposure.
	3.5.3	Analysis Aim 3A Outcomes in sustained cohort	Compare In-hospital and ND outcomes between sustained and non-sustained cohorts.	Analysis completed with findings confirmed and available to be reported.
	3.5.4	Analysis Aim 3A Outcomes in late cohort	Compare In-hospital and ND outcomes between exposure cohorts with different timings of exposure.	Analysis completed with findings confirmed and available to be reported.
	3.6.1	Analysis 3B Durations as a modifier of management (sustained cohort)	Subgroup analysis within the sustained and non-sustained cohorts and compare between different management approaches (All non-pharm vs All Rx)	Subgroup analysis completed with findings confirmed and available to be reported.
	3.6.2	Analysis 3B Timing as a modifier of management	Subgroup analysis within the exposure cohorts based on timing and compare between different management approaches: (All non-pharm vs All Rx)	Subgroup analysis completed with findings confirmed and available to be reported.

Task 4: : Dissemination of Study Results				
	Subtasks		Deliverables	Assessment Deemed Acceptable if
	4.1	Presentation of results at meetings	Abstracts to report result of research are submitted for presentations of at national meetings of professional societies or academic medicine.	Abstracts are accepted for presentation at national meetings
	4.2	Preparation of manuscripts for publication	Manuscripts are drafted and submitted for publication in peer reviewed journals	Findings are organized as manuscripts and ready for submission for publication in peer-reviewed journals.
Task 5: Project Monitoring and Team Communication				
	Subtasks		Deliverables	Assessment Deemed Acceptable if
	5.1	Monthly research team phone conferences	Virtual monthly meetings are held with participation of the entire research team to discuss research findings.	Agendas and minutes of each phone conference are maintained for documentation.
	5.2	Monthly progress reports	Study progress, challenges, and budget expenditures are summarized and submitted to FDA.	Monthly progress report of study and budget items are filed, and acknowledged
	5.3.1	First In-Person Investigators meetings	Review study progress, ensure all milestones are met, discuss problems, develop solutions, plan presentations	Meeting minutes and action items
	5.3.2	Second In-Person Investigators meetings	Review study progress, ascertain tall milestones are met, discuss problems, develop solutions, plan analysis, present & publish study results	Meeting minutes and action items
	5.3.3	Third In-Person Investigators	Review study progress, ascertain tall milestones are met, discuss problems,	Meeting minutes and action items

		meetings	develop solutions, plan analysis, present & publish study results	
	5.3.4	Fourth In-Person Investigators meetings	Review study progress, ascertain tall milestones are met, discuss problems, develop solutions, plan analysis, present & publish study results	Meeting minutes and action items
	5.3.5	Fifth In-Person Investigators meetings	Review study progress, ascertain tall milestones are met, discuss problems, develop solutions, plan analysis, present & publish study results	Meeting minutes and action items
	5.3.6	Final In-Person Investigators meetings	Review study progress, ascertain tall milestones are met, discuss problems, develop solutions, plan analysis, present & publish study results	Meeting minutes and action items

7. Gantt Chart, Work Breakdown Structure and Milestones

7.a. Gantt Chart & WBS

The responsible co-investigators, as well as the PI, are indicated in the Gantt chart with each specific WBS #. Gantt chart with Work Breakdown Structures are shown with initials of the Co-Investigators in the Gantt chart WBS are as follows

LS=Lena Sun (PI), MK= Michael Kuzniewicz (Kaiser site PI and co-investigator) CC=Cynthia Campbell and MH=Monique Hedderson (both co-investigators at Kaiser); SP=Samuel Pimentel (Lead statistician and co-investigator at Berkeley); SC=Sandra Comer (Co-investigator at Columbia); CS=Cynthia Salorio (consultant)

WBS #	TASKS	Responsible investigator(s)	Year 1				Year 2				Year 3				Year 4			
			2023	2024			2025				2026				2027			
			Sept-Dec	Jan-Mar	Apr-Jun	Jul-Sept	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sept	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sept	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Aug
1	**Prepare and planning of study**																	
1.1	Create birth cohort	LS, MK, CC, MH																
1.2	Query dataset for maternal exposures	LS, MK, CC, MH																
1.3	Query pharmacy records for maternal exposures	LS, MK, CC, MH																
1.4	Query dataset for postnatal management	LS, MK, CC, MH																
1.5	Obtain IEP and other developmental data	MK, CC, MH,CS																
1.6	Create study cohorts	LS, MK, CC, MH																
2	**Test and finalize plans for match analysis**																	
2.1	Generate and test match models	LS, MK, SP																
2.2	Select match model to use for analysis	LS, MK, SP																
3	**Data analyses of all study aims**																	
3.1.1	Analysis Aim 1A:All Non-Pharm vs All Rx	LS, MK, SP																
3.1.2	Analysis Aim 1A: ESC vs Pre-ESC Rx	LS, MK, SP																
3.1.3	Analysis Aim 1A: ESC vs Post-ESC Rx	LS, MK, SP																
3.2.1	Analysis Aim 1B: Pilot prospective study: Recruit/enroll	LS, MK, SP,CS																
3.2.2	Analysis Aim 1B: Pilot prospective study: Testing	LS, MK, SP,CS																
3.3.1	Analysis Aim 2A: Sources, dosess in NOWS cohort	LS, MK, SC, SP																
3.3.2	Analysis Aim 2A: Co-exposures in NOWS cohort	LS, MK, SC, SP																
3.3.3	Analysis Aim 2A: Create MME cohort	LS, MK, SC, SP																
3.4.1	Analysis Aim 2B: Outcomes in high MME cohort	LS, MK, SP																
3.4.2	Analysis Aim 2B: MME doses as modifier of management	LS, MK, SP																
3.5.1	Analysis Aim 3A: Durations & Create sustained exposure cohort	LS, MK, SP																
3.5.2	Analysis Aim 3A: Timing & Create timing of exposure cohorts	LS, MK, SP																
3.5.3	Analysis Aim 3A: Outcomes in sustained exposure cohort	LS, MK, SP																
3.5.4	Analysis Aim 3A: Outcomes in timing of exposure cohorts	LS, MK, SP																
3.6.1	Analysis Aim 3B: Durations as modifier of management	LS, MK, SP																
3.6.2	Analysis Aim 3B: Timing as modifier of management	LS, MK, SP																
4	**Dissemination of study results**																	
4.1	Presentation of results at meetings	LS, MK, SP, CC, MH,SC,CS																
4.2	Preparation of manuscripts to submit for publication	LS, MK, SP, CC, MH,SC,CS																
5	**Project monitoring & study team communications**																	
5.1	Monthly research team phone conferences	LS, MK, SP, CC, MH,SC,CS																
5.2	Monthly progress reports	LS																
5.3	In-Person Investigators meetings	LS, MK, SP, CC, MH,SC,CS																

7.b. Assigned WBS # for Subcontracting Site Research Personnel

WBS	KPNC					Berkeley
	Michael Kuzniewicz	Cynthia Campbell	Monique Hedderson	Dana Edelman	Sheiran Li	Samuel Pimentel
	Site PI	Co-investigator	Co-investigator	Program manager	Data Analyst	Site PI; Lead statstician
1.1	X	X	X	X	X	X
1.2	X	X	X	X	X	X
1.3	X	X	X	X	X	X
1.4	X	X	X	X	X	X
1.5	X	X	X	X	X	X
1.6	X	X	X	X	X	X
2.1	X					X
2.2	X					X

WBS	Michael Kuzniewicz	Cynthia Campbell	Monique Hedderson	Dana Edelman	Sheiran Li	Samuel Pimentel
3.1.1	X				X	X
3.1.2	X				X	X
3.1.3	X				X	X
3.2.1	X				X	X
3.2.2	X				X	X
3.3.1	X				X	X
3.3.2	X				X	X
3.3.3	X				X	X
3.4.1	X				X	X
3.4.2	X				X	X
3.5.1	X				X	X
3.5.2	X				X	X
3.5.3	X				X	X
3.5.4	X				X	X
3.6.1	X				X	X
3.6.2	X				X	X
4.1	X	X	X	X	X	X
4.2	X	X	X	X	X	X
5.1	X	X	X	X	X	X
5.2	X					X
5.3	X	X	X	X	X	X

7.c. Timeline and Milestones

Date of Completion	Milestones
6/30/2024	Complete query EHR and pharmacy record for exposures
3/31/2025	Obtain other developmental metrics Complete creation of study cohorts
9/30/2025	Finalize plans for matched analysis
12/31/2026	Complete analysis of Aim 2A Create exposure cohorts based on durations and timing
3/31/2027	Complete analysis of Aim 1A Complete analysis of Aim 2B Outcomes in exposure cohorts based on durations & timing Complete analysis of Durations as a modifier Complete analysis of Timing as a modifier
6/30/3027	Complete prospective pilot
8/31/2027	Complete project

8. DELIVERABLE SCHEDULE

8.a. Deliverable Schedule by Year

Year 1	• Finalize NOWS cohort from birth cohort (1.1) • Complete queries re maternal exposures & postnatal management (1.2, 1.3, 1.4) • Monthly team phone conference (5.1) • Monthly progress report submission to FDA (5.2) • ***Two*** In-person Investigators meetings (5.3)
Year 2	• Obtain IEP & other data re ND from non-Kaiser sources (1.5) • Finalize study cohorts based on management approaches (1.6) • Finalize match model for analysis (2.1, 2.2) • Assemble prospective cohort (3.2.1) • Presentation of results (4.1) • Monthly team phone conference (5.1) • Monthly progress report submission to FDA (5.2) • ***One*** in-person investigators meeting (5.3)
Year 3	• Characterize sources of prenatal opioid exposures (3.3.1) • Determine MME doses of prescription prenatal opioid exposure (3.3.1) • Characterize gestational timing, durations of exposures (3.4.1, 3.4.2) • Characterize co-exposures of other substances (3.3.2) • Complete data collection for prospective ND outcomes assessment (3.2.2) • Presentation of results (4.1) • Prepare manuscript (4.2) • Monthly team phone conference (5.1) • Monthly progress report submission to FDA (5.2) • ***One*** In-person investigators meeting (5.3)
Year 4	• Finalize high MME dose cohort (3.4.1) • Finalize exposure cohorts by durations & timing (3.5.1, 3.5.2) • Complete analysis of in-hospital outcomes in all study cohorts (3.1.1, 3.1.2, 3.1.3, 3.4.1, 3.5.3, 3.5.4) • Complete analysis of ND outcomes in all study cohorts (3.1.1, 3.1.2, 3.1.3, 3.4.13.5.3, 3.5.4) • Complete subgroup analysis of timing and duration of exposures as modifiers of outcomes (3.6.1, 3.6.2) • Presentation of study results (4.1) • Prepare and submit manuscripts (4.2) • Monthly team phone conference 5.1) • Monthly progress report submission to FDA (5.2) • ***Two*** In-person investigators meetings (5.3)

8.b. Detailed Deliverable Schedule with Timeline and Due Dates

Task 1: Project Planning and Preparation

Subtasks		*Timeline*	*Due Date*	*Deliverables*
1.1	**Create NOWS cohort from birth cohort**	9/2023-3/2024	3/31/2024	NOWS cohort created from birth cohort 2010-2023.
1.2	**Query dataset for maternal exposures**	9/2023-6/2024	6/30/2024	Sources of maternal opioid exposure established
1.3	**Query pharmacy records for maternal exposures**	9/2023-6/2024	6/30/2024	Maternal opioid exposure re: timing during pregnancy, durations, types of opioids and doses established. Milligrams morphine equivalent doses of prescription opioids during pregnancy calculated.
1.4	**Query dataset for postnatal management**	9/2023-6/2024	6/30/2024	Postnatal management by non-pharmacologic or opioids replacement treatment confirmed.
1.5	**Obtain IEP and other developmental data**	9/2023-3/2025	3/31/2025	All referrals for evaluations of hearing, autism, speech identified. All referrals for occupational, physical and speech therapy identified. Data re IEP referral retrieved
1.6	**Create study cohorts**	4/2024-3/2025	3/31/2025	Four different study cohorts from the NOWS cohort are created: Pre-ESC, ESC, Pre-ESC Rx and Post-ESC Rx

Task 2: Testing and Selecting Models for Analysis

Subtasks		*Timeline*	*Due Date*	*Deliverables*
2.1	**Generate and test match models**	7/2024-6/2025	6/30/2025	Generate and test different models for the matched analysis. Findings from the testing are summarized, with strengths and weaknesses of the different models identified.
2.2	**Select match model to use for analysis**	1/2025-9/2025	9/30/2025	Select final model used for match analysis

Task 3: Data Analysis of All Study Aims

Subtasks		*Timeline*	*Due Date*	*Deliverables*
3.1	**Analysis Aim 1A**			
3.1.1	Analysis Aim 1A All Non-Pharm vs All Rx	4/2025-3/2027	3/31/2027	Analysis in the NOWS cohort, derived from the entire birth cohort from 2010-2023. Completed analysis with results that either show no differences or a difference in outcomes between non-pharmacological management compared to opioids replacement pharmacotherapy.
3.1.2	Analysis Aim 1A ESC vs Pre-ESC Rx	4/2025-3/2027	3/31/2027	Analysis that compares the in-hosp outcomes and ND outcomes between ESC-managed and opioids replacement treated infants with NOWS before 2016.
3.1.3	Analysis Aim 1A ESC vs Post-ESC Rx	4/2025-3/2027	3/31/2027	Analysis that compares the in-hosp outcomes and ND outcomes between ESC-managed and opioids replacement treated.
3.2	**Analysis Aim 1B**			
3.2.1	Analysis Aim 1B Pilot prospective study: Recruit/enroll	10/2024-6/2027	6/30/2027	Contact children from each of the four cohorts: Pre-ESC, ESC, Pre-ESC Rx and Post-ESC to discuss study, and recruit study participants, and consent parents
3.2.2	Analysis Aim 1B Pilot prospective study II	10/2024-6/2027	6/30/2027	Administer testing and home environment questionnaire. Draft data collection form
3.3	**Analysis Aim 2A**			
3.3.1	Analysis Aim 2A Sources, doses in NOWS cohorts	4/2025-12/2026	12/31/2026	Determine the sources of opioid exposure in the entire NOWS cohort, and the four study cohorts
3.3.2	Analysis Aim 2A Co-exposures in NOWS cohorts	7/2025-12/2026	12/31/2026	Characterize co-exposures in the NOWS cohort, the four study cohorts. Query EHR to identify DSM-5 diagnoses of mothers of NOWS cohort and

				the high MME cohort. Characterize prescription SSRI and psychoactive medications in the NOWS cohort and high MME cohort.
3.3.3	Analysis Aim 2A: Create MME cohort	7/2025-12/2026	12/31/2026	In the group with prenatal prescription opioids, review of pharmacy records to determine doses (in MME): total cumulative, range, mean, median. The top quartile MME is denoted as the high MME cohort. Characterize co-exposures in the high MME cohort. Analysis of co exposure of prescription psychoactive medications in the high MME group.
3.4	**Analysis Aim 2B**			
3.4.1	Analysis Aim 2B: Outcomes in high MME cohort	7/2025-12/2026	12/31/2026	Compare In-hospital and ND outcomes between high MME group with the remaining MME group.
3.4.2	Analysis Aim 2B: MME doses as a modifier of management	7/2025-3/2027	3/31/2027	Subgroup analysis within the high MME and remaining MME groups comparing between different management approaches (All non-pharm vs All Rx)
3.5	**Analysis Aim 3A**			
3.5.1	Analysis Aim 3A Durations & Create sustained exposure cohort	7/2024-12/2026	12/31/2026	Determine the durations of exposures (in weeks) in the NOWS cohort. Determine the distribution of exposure durations based on number of four-week periods in the NOWS cohort and the study cohorts Denote sustained exposure cohort: ≥ 2 four week periods. All others are non-sustained exposure cohort.

3.5.2	Analysis Aim 3A Timing & Create exposure cohort based on timing of gestational exposure	7/2024-12/2026	12/31/2026	Examine the timing of exposures based on the trimester(s) of exposure. Define distribution of gestational exposure in all cohorts. Designate infants with NOWS having exposure during the third trimester as the late gestational exposure cohort. Those had exposure that began during 1st and/or 2nd trimesters as the early gestational exposure cohort
3.5.3	Analysis Aim 3A Outcomes in sustained exposure cohort	7/2024-3/2027	3/31/2027	Compare In-hospital and ND outcomes between sustained and non-sustained cohorts
3.5.4	Analysis Aim 3A Outcomes in exposure cohorts based on timing	7/2024-3/2027	3/31/2027	Compare In-hospital and ND outcomes between late gestational and early gestational exposure cohorts,
3.6	**Analysis Aim 3B**			
3.6.1	Analysis 3B Durations as a modifier of management (sustained cohort)	7/2024-3/2027	3/31/2027	Subgroup analysis within the sustained and non-sustained cohorts and compare between different management approaches (All non-pharm vs All Rx)
3.6.2	Analysis 3B Timing as a modifier of management	7/2024-3/2027	3/31/2027	Subgroup analysis within the late gestational exposure and early gestational exposure cohorts and compare between different management approaches: (All non-pharm vs All Rx)

Task 4: Dissemination of Study Results

Subtasks		*Timeline*	*Due Date*	*Deliverables*
4.1	**Presentation of results at meetings**	4/2025-8/2027	8/31/2027	Abstracts to report result of research are submitted for presentations of at national meetings of professional societies or academic medicine.
4.2	**Preparation of**	7/2025-	8/31/2027	Manuscripts are drafted and

	manuscripts for publication	8/2027		submitted for publication in peer reviewed journals

Task 5: Study Team Communication and Project Monitoring

Subtasks		*Timeline*	*Due Date*	*Deliverables*
5.1	**Monthly research team phone conferences**	9/2023-8/2027	Monthly	Virtual monthly meetings are held with participation of the entire research team are held each month to discuss research findings.
5.2	**Monthly progress reports**	Monthly 9/2023-8/2027	By 15th of each month	Study progress, challenges, and budget expenditures are summarized and submitted to FDA.
5.3	**In-Person Investigators meetings**			
5.3.1	First In-Person Investigators meetings	9/2023-12/2023	12/31/2023	Review study progress, ascertain tall milestones are met, discuss problems, develop solutions, plan analysis, present & publish study results
5.3.2	Second In-Person Investigators meetings	7/2024-9/2024	9/2024	Review study progress, ascertain tall milestones are met, discuss problems, develop solutions, plan analysis, present & publish study results
5.3.3	Third In-Person Investigators meetings	4/2025-6/2025	6/2025	Review study progress, ascertain tall milestones are met, discuss problems, develop solutions, plan analysis, present & publish study results
5.3.4	Fourth In-Person Investigators meetings	1/2026-3/2026	3/2026	Review study progress, ascertain tall milestones are met, discuss problems, develop solutions, plan analysis, present & publish study results

5.3.5	Fifth In-Person Investigators meetings	10/2026-12/2026	12/2026	Review study progress, ascertain tall milestones are met, discuss problems, develop solutions, plan analysis, present & publish study results
5.3.6	Sixth and Final In-Person Investigators meetings	7/2027-8/2027	8/2027	Review study progress, ascertain tall milestones are met, discuss problems, develop solutions, plan analysis, present & publish study results

9. SECURITY PLANNING

Data abstracted and datasets compiled for the for the study will reside on Kaiser Permanente Division of Research Severs in folders only accessible to the study team and on a secure, password-protected KP server behind a firewall at the Division of Research. Only PHI relevant to the study will be extracted. Study identification numbers will be assigned so that medical record numbers can be stripped from the dataset whenever feasible. PHI will only be utilized for purposes of data cleaning and auditing. De-identification will take place once all linkages are performed and data is validated and cleaned. Identifiers will be removed from datasets during the de-identification process. Data will be de-identified as soon as it is feasible. All analyses will occur within the KPNC firewall following standard procedures in place at the Division of Research. Summary data of results will be shared with team members outside of Kaiser Permanente, but all raw data will reside on the KP servers. Sam Pimentel PhD (UC Berkeley) will be granted authorization to access the study when physically at the DOR to direct the analytic plan. No data will be removed from KP DOR servers.

For the prospective pilot study, research team members at Kaiser will identify potential study participants, then contact each potential study participant to discuss the study, assess eligibility, recruit, consent and enroll. For each study participant, assessment will be performed either on site at one of the Kaiser facilities or virtually or by phone. All study related data from EHR and the results will be deidentfied, and entered into a data collection form for further analyses.

The performance site at Columbia University is PH5-544, which has card-key restricted access. De-identified data and summary results from analysis of the study and all other study-related information will be additionally encrypted before saved on desktop computers or mobile devices. All desktops, laptop computers and mobile devices will be password protected.

10. INTELLECTUAL PROPERTY

No issued patents or published patent applications will be used in the performance of the contract. The Offeror's research team at Columbia University and Kaiser Permanente Northern California will have intellectual ownership of the work product derived from the proposed contract. The final ownership will be negotiated between the two entities.

11. BIOGRAPHICAL SKETCHES

Lena S. Sun, MD. Role: PI

Over the past decade, Dr. Sun's research has focused on neurodevelopmental outcome studies in children who had early childhood exposure to anesthesia. As the leader and PI of the Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) project, she worked closely with an interdisciplinary team to examine anesthesia and neurodevelopment in children. Her clinical background as a pediatrician, an anesthesiologist, her research background related to prenatal exposure to cocaine and neurodevelopmental outcome as well as her track record to lead an interdisciplinary research team will importantly contribute to the knowledge and skills needed to successfully complete the proposed study.

Sandra Comer, PhD. Role: Co-investigator

Dr. Sandra Comer is a Professor of Neurobiology (in Psychiatry) at Columbia University Medical Center (CUMC), a Research Scientist at the Research Foundation for Mental Hygiene, Inc. (RFMH) and at the New York State Psychiatric Institute (NYSPI). She has been performing substance abuse research with opioids. Dr. Comer has worked on projects designed to examine the relative abuse liabilities of opioid medications, including an existing study that was funded recently by the FDA. Dr. Comer has a broad background in substance abuse medications development research using a variety of drug self-administration paradigms in both laboratory animals and humans, with specific expertise in opioid use disorders (OUD). Over the past 25 years, she has been a PI or Co-PI on several human laboratory proof-of-concept trials of new medications. Of relevance to the proposed project are studies that she has completed using models of opioid withdrawal in human research volunteers.

Michael Kuzniewicz, MD. MPH. Role: Site PI at Kaiser

Dr. Michael Kuzniewicz is the director of the Perinatal Research Unit at Kaiser Permanente Northern California, where each year >40,000 births/year are followed for short- and long-term outcomes in neonates (such as cerebral palsy and autism spectrum disorders), going back as far as 1995. He has utilized the data from the Kaiser Permanente database and has significant experience on how to acquire data from Kaiser Permanente's integrated electronic databases. He has been responsible for overseeing the maintenance and updating of data collection efforts as the director of the Perinatal Research Unit. Thus, he is uniquely positioned to facilitate the

acquisition of the necessary data elements for this project. As a practicing neonatologist, Dr. Kuzniewicz brings the clinical perspective in thinking about the clinical risk factors in the neonatal period that may confound the outcomes that will be studied in this proposal

Cynthia Campbell, PhD. Role: Co-investigator

Dr. Cynthia Campbell is a senior research scientist at the Division of Research, Kaiser Permanente Northern California. She has been conducting research related to substance use and comorbidity for 20 years, using pragmatic trials, patient surveys, and electronic health record data. Her work has focused largely on prescription opioid use and misuse and co-occurring psychiatric and medical conditions. She has studied longitudinal trends of substance use and the impact of health policy on access to substance use treatment, including for women with substance use disorder and the impact of cannabis use on obstetric and child developmental outcomes. She is the Contact PI (MPI Bradley) of the Health Systems Node of the NIDA Clinical Trials Network (CTN); the node focuses on integrating care for addiction into medical settings and conducting research as embedded researchers in learning health care systems. She has collaborated successfully with the research team in previous studies examining opioid use in pregnant women, and this important research builds on that work. She will contribute to successful execution of the proposed study aims.

Monique Hedderson, PhD, Role: Co-investigator

Dr. Monique Hedderson is senior research scientist and an epidemiologist at the Division of Research, Kaiser Permanente Northern California. Her research portfolio investigates the influence of preconception, prenatal and early childhood exposures on maternal and child health. She is a well-established addiction researcher. Her work includes developing methods to quantify maternal opioids use. As a member of the research team, she will contribute her wide- ranging content expertise in this area. In addition, she will bring her extensive experience in the use of the KPNC database specifically related to examining maternal opioids and other substances use in the proposed study.

Samuel Pimentel, PhD. Role: Site PI at UC Berkeley

Dr. Samuel Pimentel, an assistant professor at UC Berkley. His research focuses on developing and applying statistical methods for estimating causal effects in observational datasets, including administrative records and large electronic health databases. He is the Principal Investigator for NSF CAREER award #2142146, which supports his work on modernizing matching and weighting methods for large administrative datasets. His work has been published in leading statistical journals such as the *Journal of the American Statistical Association*, *Biometrika*, and *The Annals of Applied Statistics*. His software packages for matching in R, rcbalance and matchMulti, are widely used in practice. He has extensive experience collaborating with diverse teams of clinical and policy researchers on problems in health services

research. He will lead in the design, analysis, and reporting of matched comparisons and effect estimates, and supervise and direct the graduate student supported by the grant in their implementation of these comparisons and be a co-author articles for publication in peer-reviewed journals.

Cynthia Salorio, PhD. Role: Consultant

Dr. Cynthia Salorio, Associate Professor of Physical Medicine and Rehabilitation at Johns Hopkins School of Medicine and Co-Director, Department of Neuropsychology at Kennedy Krieger Institute. She substantial clinical and research experience, in neurodevelopmental outcomes after early brain insult in children. She has been the neuropsychology expert who oversaw the outcomes measurement and study design for several multicenter studies, including examining developmental outcomes in children with early anesthesia exposure (PANDA) and children who have undergone extracorporeal membrane oxygenation (ECMO/BEAM). Dr. Salorio will serve as a consultant and recommend the assessment instruments for the prospective study and assist in the interpretation of the results from the assessments.

12. LIST OF THE LAST 3 RELATED CONTRACTS DURING THE PAST 3 YEARS

Name of Contracting Organization: Food and Drug Administration
Contract Number: 75F40120D00039
Contract Type: Fixed Price Contract
Total Contract Value: $4,375,540
Description of Requirement: OHDSI-based FDA BEST Community Engagement and Development Coordination Center
Contracting Officer's Name and Telephone Number: Nick Sartain; (870) 543-7370
Program Manager's Name and Telephone Number: N/A
NAICS Code: 611310

Name of Contracting Organization: Duke University Medical Center (via Food and Drug Administration)
Contract Number: DUMC A034238 (FDA contract # 75F40120C00179)
Contract Type: Cost Reimbursement Contract
Total Contract Value: $50,000
Description of Requirement: QUANTIFYING PATIENTS' BENEFIT-RISK TRADEOFFS ASSOCIATED WITH PERCUTANEOUS REVASCULARIZATION OPTIONS FOR PERIPHERAL ARTERIAL DISEASE: A COLLABORATIVE EFFORT WITH THE RAPID PATHWAYS PATIENT SCIENCE WORKING GROUP
Contracting Officer's Name and Telephone Number: Thushi Amini; Thushi.Amini@fda.hhs.gov
Program Manager's Name and Telephone Number: N/A
NAICS Code: 611310

Name of Contracting Organization: University of St. Gellen (via Food and Drug Administration)
Contract Number: USG 11-21 (FDA contract # 75F40121C00161)
Contract Type: Cost Reimbursement Contract
Total Contract Value: $148,659
Description of Requirement: RiskSurve-Towards a holistic riskbased Site Surveillance An approach for remote, data-based site risk identification and inspection preparation in a (post-) Covid Environment
Contracting Officer's Name and Telephone Number: Kimberly DeLong; Kimberly.Delong@fda.hhs.gov
Program Manager's Name and Telephone Number: N/A
NAICS Code: 611310